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Original Article

Sleep disorders increase the risk of venous thromboembolism in individuals without sleep apnea: a nationwide population-based cohort study in Taiwan

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ABSTRACT

Objective: Studies investigating the relationship between sleep disorders (SDs) and the risk of venous thromboembolism (VTE) are scarce. The present study from Taiwan evaluated whether the risk of VTE was associated with SDs other than sleep apnea.
Methods: The present study investigated the incidence and risk of VTE in 46,371 people with SDs, compared with 92,742 controls without SDs. The follow-up period began from the date of entering the study cohort to the date of a VTE event, censoring, or December 31, 2011. A Cox proportional hazards regression analysis was conducted to estimate the effects of SDs on the risk of VTE.
Results: The SD cohort had a 1.79-fold adjusted hazard ratio (HR) of subsequent VTE, compared with the non-SD cohort (95% CI 1.49–2.16). The incidence of VTE increased with age for both cohorts but was higher for those in the SD cohort. However, the adjusted HRs for VTE were significantly higher for the people with SDs aged ≦49 years (HR 3.29, 95% CI 2.12–5.12) and 50–64 years (HR 2.43, 95% CI 1.76–3.35), but were not significant for the oldest group (HR 1.11, 95% CI 0.84–1.47), compared with the controls. The multiplicative increased risk of VTE was significant for the people with SDs with any comorbidity.
Conclusion: This nationwide cohort study determined that the VTE risk significantly increased in people with SDs compared with those of the general population.

1. Introduction

Insomnia is a common, worldwide complaint [1–3]; it is also a common sleep disorder (SD) that is characterized by difficulty falling and staying asleep. The association between SDs and comorbidities such as previous psychiatric disorders, circulatory diseases, and gastrointestinal diseases is evident [1]. Several studies have reported that insomnia may predispose people to a risk of cardiovascular and cerebrovascular events [4–6].

Deep vein thrombosis (DVT) is the formation of blood clots in one or more of the deep veins, possibly causing a blood clot to break loose, travel through the bloodstream, and lodge in the lungs. Pulmonary thromboembolism (PE) is a potentially life-threatening disorder involving embolic or thrombotic occlusion of the pulmonary arterial system. Combined, DVT and PE constitute venous thromboembolism (VTE), which is a catastrophic disease and has a 30-day case fatality rate of 11–30% [7–9]. Atherothrombosis and VTE share common risk factors and pathophysiological characteristics of inflammation, endothelial injury, and hypercoagulability.

Multiple acquired risk factors are associated with VTE development. The VTE incidence in immobilized post-cerebrovascular accidents (CVAs) is relatively high [10]. Leg fractures and major surgery are also critical risk factors for VTE [11], and the risk of VTE

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increases among people with spinal cord injuries as well [12]. In addition, numerous cancers have also been shown to correlate with VTE [13,14].

A SD may drive inflammation and elevate the inflammatory mediators [15], and inflammation involves endothelial dysfunction and coagulopathy [16]. Among people with VTE, the prevalence of obstructive sleep apnea appears to be higher than in the general population [17]. However, SD is not a traditional risk factor for VTE, and studies investigating the possibility that SD may increase VTE risks have been few. A longitudinal, nationwide cohort study was conducted in Taiwan in order to investigate whether people with SDs other than sleep apnea had an increased risk of subsequent VTE development.

2. Methods

2.1. Data sources

The National Health Insurance (NHI) program was launched in Taiwan in 1995, and since then has contracted 97% of medical providers and enrolled up to 99% of the Taiwanese population. The National Health Research Institute (NHRI) is responsible for managing insurance claims data, which contains all medical claims from 1996 to 2011. The NHRI has established electronic datasets for administrative and research purposes. The National Health Insurance Research Database (NHIRD) has been described in detail in previous studies [18,19]. The present study used a sub dataset of the NHIRD, which comprises one million randomly sampled beneficiaries enrolled in the NHI program in 2000, and involved collecting all of the records of the study participants from the period 1996–2011.

The diagnosis codes used in the NHRI are based on the International Classification of Diseases, Revision 9, Clinical Modification (ICD-9-CM). The World Health Organization published ICD-9-CM for clinical classification purposes as well as for death certificates [20]. The NHRI encrypts the personal information of people, for privacy protection, and provides researchers with anonymous identification numbers associated with the relevant claims information, including gender, date of birth, registry of medical services, and medication prescriptions. Individual consent is not required for accessing the NHIRD. The Institutional Review Board of China Medical University in Central Taiwan exempted this study (CMU-REC-101-012).

2.2. Study participants

The present study consisted of a cohort of people with SDs and a comparison cohort without SDs. Newly diagnosed people with non-apnea SD were identified in the database between January 1 1998 and December 31 2001 (ICD-9-CM 307.4 and 780.5). The index date was defined as the date of first diagnosis of SD. People with a history of VTE (ICD-9-CM 415.1 and 453.8), except for iatrogenic PE (ICD-9-CM 415.11) or sleep apnea syndrome (ICD-9-CM 780.51, 780.53 and 780.57) before the index date, and those aged younger than 18 years were excluded. For each corresponding person with a SD, four controls without SD were selected using a systematic random-sampling method as a comparison cohort, and they were frequency matched by age, gender, and index year, according to the same exclusion criteria. Finally, a total of 46,371 people with a SD and 92,742 controls without a SD were included in the present study.

2.3. Outcome measurement

The primary outcome, obtained from hospitalization records, was newly diagnosed DVT or PE. Each study participant was followed up until: a diagnosis of VTE was made, censorship for loss to follow-up, death, withdrawal from the database, the end of 2011 – whichever came first. Nearly all of the people with DVT and PE underwent comprehensive examinations before receiving intensive care. In Taiwan, the medical reimbursements and discharge notes of the patients were scrutinized in a peer-review process.

2.4. Exposure variables

In addition to a SD, the demographic characteristics such as gender, age, monthly income, occupation, medication of zolpidem and benzodiazepine (BZD), and comorbidities were analyzed. For other comorbid diseases, searches were conducted for a history of: hypertension (ICD-9-CM 401–405); diabetes (ICD-9-CM 250); hyperlipidemia (ICD-9-CM 272); CVA (ICD-9-CM 430–438); heart failure (ICD-9-CM 428); lower leg fracture or surgery (ICD-9-CM 820, 821, 823, 81.51, 81.52, 81.53, and 81.54); or malignancy (ICD-9-CM 140–208). For insurance premium estimation, the participants' monthly incomes were classified into three groups with monthly pay of: < NTD15,000; NTD15,000–19,999; and ≥NTD20,000 (USD1.0 equals approximately NTD30 [New Taiwan Dollars]). White-collar workers were defined as people who perform professional, managerial or administrative work. Typically, a white-collar worker executes his/her work in an office. Blue-collar workers were defined as people who perform manual labor, such as fishermen, farmers, and industrial laborers. Other occupations primarily included were retired, unemployed, or low-income populations.

2.5. Statistical analysis

Data analysis was performed to compare the distributions of age, gender, and comorbidities between the SD and non-SD cohorts, which were examined using the Chi-squared test. The follow-up person-years were used for estimating the incidence density of VTE. Univariable and multivariable Cox proportional hazards regression analyses were used to determine the effects of SDs on the risks of VTE, shown according to hazard ratio (HR) and 95% CI. The Kaplan–Meier method was used to estimate the VTE-free survival curve of both cohorts, and the log-rank test was used to calculate whether significant differences existed.

All of the analyses were performed using SAS statistical software (version 9.2; SAS Institute, Inc., Cary, NC, USA), and the results were statistically significant when the two-tailed *p*-values were less than 0.05.

3. Results

3.1. Comparisons of the demographic characteristics and comorbidities between the people with sleep disorders and the comparison cohort

Table 1 displays the distribution of the demographic characteristics and comorbidities of the people with SDs and the controls. Among the people in the SD cohort, 63.5% were women and 47.4% were aged younger than 49 years. The SD cohort exhibited a higher proportion of having a low income (26.1% vs 25.9%) and blue-collar jobs (39.8% vs 38.4%) than the comparison cohort. Compared with the people in the comparison cohort, people with SDs exhibited significantly higher rates of: hypertension (39.1% vs 24.5%, $p < 0.0001$); diabetes (15.1% vs 10.1%, $p < 0.0001$); hyperlipidemia (20.4% vs 10.9%, $p < 0.0001$); CVAs (14.8% vs 7.44%, $p < 0.0001$); heart failure (2.43% vs 1.39%, $p < 0.0001$); lower leg fracture or surgery (1.08% vs 0.64%, $p < 0.0001$); and cancer (4.74% vs 3.08%, $p < 0.0001$).

Table 1
Comparisons of the demographic characteristics and comorbidities in people with sleep disorders and without sleep disorders.

	Sleep disorder		*p*-value
	No (*N* = 92,742)	Yes (*N* = 46,371)	
Gender			
Women	58,940 (63.5)	29,470 (63.5)	0.99
Men	33,802 (36.5)	16,901 (36.5)	
Age stratified			
≤49	43,936 (47.4)	21,968 (47.4)	0.99
50–64	24,928 (26.9)	12,464 (26.9)	
65+	23,878 (25.8)	11,939 (25.8)	
Age, mean ± SD[a]	52.0 ± 16.4	52.2 ± 16.3	0.05
Monthly income (NT$)[b]			<0.0001
<15,000	24,027 (25.9)	12,121(26.1)	
15,000–19,999	45,334 (48.9)	23,406 (50.5)	
≥20,000	23,381(25.2)	10,844 (23.4)	
Occupation			<0.0001
White collar	43,198 (46.6)	19,987 (43.1)	
Blue collar	35,616 (38.4)	18,453 (39.8)	
Others[c]	13,928 (15.0)	7931 (17.1)	
Comorbidity			
Hypertension	22,759 (24.5)	18,137 (39.1)	<0.0001
Diabetes	9393 (10.1)	7171 (15.5)	<0.0001
Hyperlipidemia	10,099 (10.9)	9464 (20.4)	<0.0001
CVA	6898 (7.44)	6839 (14.8)	<0.0001
Heart failure	1291 (1.39)	1129 (2.43)	<0.0001
Lower leg fracture or surgery	590 (0.64)	499 (1.08)	<0.0001
Cancer	2855 (3.08)	2199 (4.74)	<0.0001

[a] *t*-test. Chi-Squared Test.
[b] New Taiwan Dollars per month. One New Taiwan Dollar equals US$0.03.
[c] Other occupations primarily included retired, unemployed, or low-income populations.
CVA, cerebrovascular accident.

3.2. The incidence and hazard ratios of VTE for both cohorts by demographic characteristics and comorbidity

Table 2 shows the incidence rate of VTE for both cohorts, and the HRs of the SD cohort compared with those of the non-SD cohort, according to gender, age, and comorbidity. The incidence rate of VTE was 1.64-fold higher in the SD cohort than in the non-SD cohort (6.05 vs 3.70 per 10,000 person-years), with an adjusted HR of 1.79 (95% CI 1.49–2.16).

The gender-specific incidence shows that women with SDs have the highest risk of developing VTE (6.67 per 10,000 person-years) in both cohorts, yielding a SD to non-SD cohort HR of 2.19 (95% CI 1.74–2.74) among the women. The incidence of VTE increased with age for both cohorts and was higher for those with SD; the highest was in the oldest group. However, after this was adjusted for covariates, the age-specific SD to non-SD cohort HRs were significantly higher for those aged ≦49 years, with an adjusted HR of 3.29 (95% CI 2.12–5.12), and 50–64 years, with an adjusted HR of 2.43 (95% CI 1.76–3.35), but was nonsignificant for the oldest group, with an adjusted HR of 1.11 (95% CI 0.84–1.47) (Table 2). Moreover, compared with the non-SD cohort, the SD cohort was associated with a significantly higher risk of VTE, with an adjusted HR of 2.48 (95% CI 1.74–3.54), in those who did not present with any comorbidity.

3.3. The interaction on the risk of VTE among sleep disorders, comorbidity and medication of zolpidem and benzodiazepine

The interaction measurements between SDs and any comorbidity on the risk of VTE are shown in Table 3. Compared with those without SDs or comorbidities, the people without SDs with comorbidities exhibited a 2.09-fold risk of developing VTE (95% CI 1.62–2.70) and the highest risk was for those with both SDs and comorbidities (adjusted HR 3.37, 95% CI 2.52–4.51). Furthermore, Table 3 indicates that the risk of developing VTE in people with SDs without comorbidities exhibited a relative decrease when they received treatment (adjusted HR 2.31, 95% CI 1.86–2.88 for people receiving zolpidem treatment and adjusted HR 2.16, 95% CI 1.46–3.20 for those receiving benzodiazepine treatment).

3.4. Probability free of VTE for people with or without sleep disorders during follow-up

Fig. 1 shows the Kaplan–Meier curve of VTE-free survival for those with SDs and those without SDs. The results indicate that the VTE-free rate was significantly lower for those with SDs than for the non-SD cohort (log-rank $p < 0.0001$).

Table 2
Comparison of the incidence and hazard ratios of VTE for both cohorts by demographic characteristics and comorbidity.

	Sleep disorder							
	No			Yes				
	Event	PY	Rate[a]	Event	PY	Rate[a]	Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)
All	350	946,206	3.70	294	486067	6.05	1.64(1.40, 1.91)***	1.79(1.49, 2.16)***
Sex								
Women	216	615,086	3.51	212	317887	6.67	1.90(1.57, 2.30)***	2.19(1.74, 2.74)***
Men	134	331,120	4.05	82	168180	4.88	1.20(0.92, 1.59)	1.20(0.86, 1.66)
Stratify age								
≤49	48	478,104	1.00	78	244941	3.18	3.17(2.21, 4.55)***	3.29(2.12, 5.12)***
50–64	115	267,982	4.29	112	134459	8.33	1.94(1.50, 2.52)***	2.43(1.76, 3.35)***
65+	187	200,120	9.34	104	106667	9.75	1.04(0.82, 1.32)	1.11(0.84, 1.47)
Comorbidity[d]								
No	124	657,553	1.89	75	240999	3.11	1.65(1.24, 2.20)***	2.48(1.74, 3.54)***
Yes	226	288,653	7.83	219	245068	8.94	1.14(0.95, 1.38)	1.57(1.26, 1.94)***

[a] Incidence rate, per 10,000 person-years.
[b] Relative hazard ratio.
[c] Multivariate analysis including age, sex, monthly income, occupation, medication of zolpidem and BZD and comorbidities of hypertension, diabetes, hyperlipidemia, CVA, heart failure, lower leg fracture or surgery and cancer.
[d] Patients with any one of the comorbidities such as hypertension, diabetes, hyperlipidemia, CVA, heart failure, lower leg fracture or surgery and cancer were classified as the comorbidity group.
***$p < 0.001$.
PY, person-years.

Table 3
Cox proportional hazards regression analysis for interaction of sleep disorders and comorbidity on risk of VTE

Variable		N	PY	Event	Rate[e]	Adjusted HR (95% CI)	*p*-value
SD	Comorbidity[d]						0.035
No	No	61660	657553	124	1.89	1 (Reference)[a]	
No	Yes	31082	288653	226	7.83	2.19 (1.69, 2.84)***	
Yes	No	21777	240999	75	3.11	2.42 (1.77, 3.30)***	
Yes	Yes	24594	245068	219	8.94	3.37 (2.52, 4.51)***	
SD	Zolpidem						<0.0001
No	No	77136	788434	277	3.51	1 (Reference)[b]	
No	Yes	15606	157772	73	4.63	0.92 (0.70, 1.20)	
Yes	No	14899	151190	132	8.73	2.31 (1.86, 2.88)***	
Yes	Yes	31472	334877	162	4.84	1.06 (0.86, 1.31)	
SD	BZD						0.09
No	No	51989	531688	147	2.76	1 (Reference)[c]	
No	Yes	40753	414518	203	4.90	1.17 (0.94, 1.45)	
Yes	No	6193	63133	32	5.07	2.16 (1.46, 3.20)***	
Yes	Yes	40178	422934	262	6.19	2.01 (1.60, 2.54)***	

[a] Adjusted HR was calculated by Cox proportional hazard regression and adjusted for age, sex, monthly income, occupation, medication of zolpidem and BZD.
[b] Adjusted HR was calculated by Cox proportional hazard regression and adjusted for age, sex, monthly income, occupation, medication of BZD and comorbidities.
[c] Adjusted HR was calculated by Cox proportional hazard regression and adjusted for age, sex, monthly income, occupation, medication of zolpidem and comorbidities.
[d] People with any one of these comorbidities: hypertension, diabetes, hyperlipidemia, CVA, heart failure, lower leg fracture or surgery, and cancer were classified as the comorbidity group.
[e] Incidence rate, per 10,000 person-years.
***$p < 0.001$.
BZD, benzodiazepine; PY, person-years.

4. Discussion

Previous studies have reported that 25% of adults in Taiwan experience insomnia and that the prevalence of insomnia increases as age increases [3,21], which is consistent with studies conducted in other countries [2,22,23]. Several cohort studies have indicated that insomnia symptoms are associated with an increased risk of cardiovascular diseases [24–27]. However, these studies have not objectively assessed sleep apnea and, thus, the contribution of non-apnea SD to the increased risk of cardiovascular diseases could not be controlled for. Recent studies have determined that non-apnea SD increases the risk of subsequent acute coronary syndrome and ischemic stroke development [4,24,28].

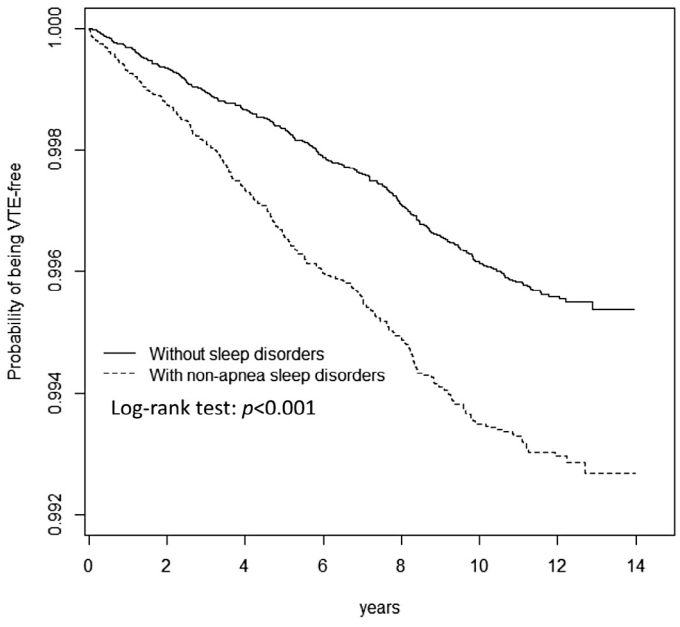

Fig. 1. Probability free of venous thromboembolism (VTE) for people with sleep disorders (dashed line) or without (solid line) sleep disorders.

The relationship between SDs and VTE has yet to be investigated. To the best of the authors' knowledge, this is the first study to investigate whether non-apnea SD increases the risk of developing VTE, by applying a longitudinal population-based cohort study in an Asian population. The present study determined that people with non-apnea SDs exhibit a 47% increased risk of VTE development, compared with the general population, after adjusting for age, gender, and comorbidities.

The mechanisms underlying the epidemiological association between non-apnea SD and VTE remain unclear. One possible theory is that non-apnea SD may contribute to systemic inflammation and vascular vulnerability. Numerous studies have reported that SDs are associated with inflammatory responses [29–31]. Inflammation may initiate clotting, decrease the activity of the natural anticoagulant mechanisms, and impair the fibrinolytic system [32]. In addition, inflammation causes widespread endothelial dysfunction [33]. When the interactions between inflammation-coagulation and inflammation-endothelial dysfunction overwhelm the natural defense systems, catastrophic events may occur, such as those manifested in VTE.

The people with non-apnea SDs exhibited a higher prevalence of comorbidities and coexistent conditions associated with the development of VTE than those in the comparison cohort. Non-apnea SD remained an independent risk factor for developing VTE after covariates were controlled for.

Most of the people in the non-apnea SD cohort in the present study were women. Numerous studies have observed a female preponderance of insomnia [34]. After adjusting for age and other comorbidities in the present study, it was observed that women with non-apnea SDs exhibited a 1.76-fold increased risk of developing VTE compared with those without SDs. In addition, the incidence rate of VTE increased as age increased for both cohorts. However, after gender and comorbidities were adjusted for, the risk of VTE was the highest for young adults among the people with non-apnea SD, suggesting that SDs exert the highest effect on the health of the young adults.

The people with non-apnea SDs exhibited significantly higher risks of subsequent VTE development compared with the controls, regardless of the existence of comorbidities. Moreover, the people with non-apnea SDs and any comorbidity exhibited

multiplicative risks of developing VTE, compared with the controls without any comorbidity.

A significant difference was observed in the VTE occurrence between the non-apnea SD cohort and comparison cohort during follow-up. Maintaining an adequate sleep duration and quality by practicing optimal sleep habits and treating SDs may reduce the risk of VTE and increase wellness.

Several limitations must be considered when interpreting these findings. First, the NHIRD does not provide detailed lifestyle information, such as body mass index, physical activity levels, and family history, all of which are potential confounding factors in the present study. However, these factors may be randomly distributed in these two large cohorts. Second, the lack of data on objective sleep measurements or other mental health conditions that are highly comorbid with SDs, and on medication history, may be a critical limitation. Finally, the lack of drug-treatment data, such as those on hormone-replacement therapy and the use of contraceptives and anticoagulant drugs, may have influenced the primary outcomes of the present study.

The present study is the first to provide epidemiologic data with which to address the association between non-apnea SD and VTE. The strength of the present study is that it provides a nationwide, population-based-cohort longitudinal study for the Asian population with which to investigate the relationship between non-apnea SD and the increased risk of subsequent VTE events. Moreover, the study population was obtained from physicians' diagnoses. The findings of the present study may benefit from additional analyses in future studies regarding which specific SDs contribute to VTE incidence.

In summary, this study was determined that people with non-apnea SDs are at a higher risk of developing VTE. Because the number of people with non-apnea SDs is progressively increasing, the enhancement of sleep-disorder management may be important for decreasing VTE events.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.07.031.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.sleep.2014.07.031.

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